Our Thanks to Ortho Pharmaceutical Corporation

We recognize with appreciation Ortho Pharmaceutical Corporation for pledging support to the Endowment Fund for The Journal of Investigative Dermatology, *which will be used to support the growth and continued success of the Journal. This support will certainly strengthen and perpetuate the partnership between the pharmaceutical industry and basic and clinical investigators in cutaneous biology.*

We salute Ortho Pharmaceutical Corporation for their contribution to the Endowment Fund and for their continued support of clinical and investigative dermatology.

D.A.N., Denver, CO

In This Issue . . .

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Melanocyte Destruction and Repopulation in Vitiligo: Additional Perspectives

Vitiligo is a common and complex depigmentary disorder extensively studied in man and in animal models. What is the mechanism for pigment-cell destruction in vitiligo? There is evidence for the contribution of immunologic, autocytotoxic, neuronal, and environmental factors in the melanocyte damage that characterizes vitiligo. It has been long proposed that inherent melanocyte abnormalities precede the cellular destruction which produces depigmentation. The other important question in vitiligo research is, What is the mechanism of repigmentation of vitiliginous patches, which can be induced by photochemotherapy and perhaps by other treatments under current investigation? In this issue are three papers that consider different aspects of melanocyte biology relevant to depigmentation and repigmentation in vitiligo.

Boissy and his colleagues at the University of Cincinnati have established long-term melanocyte cultures from 14 patients with vitiligo and analyzed the cells ultrastructurally. The cultures from three quarters of the patients developed ultrastructural abnormalities characterized by dilation of the rough endoplasmic reticulum, circular RER profiles, and/or membrane-bound compartments of melanosomes. Similar abnormalities were rarely seen in cultures from normal subjects. The ultrastructural abnormalities were seen in melanocytes from patients with active disease, with stable disease, or in repigmenting patients. The authors note that "these results indicate that the inherent melanocyte abnormality may not be solely responsible for the selective elimination of these cells from the vitiligo epidermis," and speculate that the altered communication of these melanocytes with their epidermal environment may induce other factors such as cytokines, adhesion molecule, and/or an immunologic response that results in selective melanocyte destruction.

The relative susceptibility of melanocytes to toxic and immunologic damage has been proposed as an important determinant in melanocyte damage in vitiligo, and as a secondary phenomenon in cutaneous inflammation. Yohn and co-workers from the University of Colorado have analyzed antioxidant defenses of cultured normal human melanocytes and compared them to the profile of antioxidant defenses in cultured human fibroblasts and keratinocytes. They found significantly lower levels of catalase, superoxide dismutase, and glutathione peroxidase in cultured human melanocytes. The levels of these enzymes were not different in cells cultured from Black versus Caucasian foreskins. The authors propose that inherently lower antioxidant defenses may be a key component in the relative susceptibility of melanocytes to oxidant stress produced following ultraviolet radiation or inflammation, and may contribute to the cellular damage seen during vitiligo. These two papers support the hypothesis that melanocytes in vitiligo are susceptible to toxic damage based on intrinsic melanocyte deficits in antioxidant defenses and also on more individually determined defects seen in vitiligo patients.

In this issue Cui, Shen, and Wang from Beijing Medical University have studied the dynamics of melanocyte repopulation of vitiliginous skin using histochemical and ultrastructural techniques. They confirmed previous work demonstrating repigmentation of vitiliginous skin from the hair follicle, documenting the presence of a reservoir of DOPA-negative ("inactive") melanocytes in the outer root sheath of hair follicles. Treatment stimulated these cells in the middle and lower regions of the outer root sheath to divide and migrate upward along the surface of the outer root sheath to the epidermis, where they continued to migrate radially to form the pigmented island visible in vitiligo patients. This study sets the stage for future work to define the pharmacologic and mechanistic basis for the proliferation and migration of melanocytes into depigmented epidermis.

Allergen-Specific T Lymphocytes in the Pathogenesis of Atopic Dermatitis

Patients with atopic dermatitis have a high incidence of immediate hypersensitivity reactions and elevated serum IgE levels, but the cellular infiltrates in their skin lesions show lymphocytic and monocytic infiltrates in the dermis. Are these patients reacting to allergens which stimulate both lymphocyte- and IgE-dependent immune responses? How are humoral and cellular immunity linked in these patients?

In this issue van der Heijden and his colleagues at the University

0022-202X/91/$03.50

of Amsterdam have approached this question by analyzing cytokine production by cloned lymphocytes from atopic dermatitis lesions. Peripheral blood lymphocytes and cloned lesional T lymphocytes from two patients allergic to house dust mite antigens were stimulated in vitro with mite antigens. The authors then compared the allergen reactivity and subsequent cytokine production of peripheral blood lymphocytes to those of T lymphocytes cloned from skin lesions. They found that a very high percentage of IL-4 – producing CD4+ allergen-specific T lymphocytes in the lesional skin compared to the peripheral blood. This supports the hypothesis that the allergen is causing selective recruitment or expansion of allergen-reactive lymphocyte populations in the lesion skin. They also found that IL-4 produced by these stimulated lymphocytes could induce the expression of the low-affinity IgE receptor (CD23) on antigen-presenting cells. Langerhans cells in the epidermis of atopic dermatitis show enhanced expression of CD23, and IL-4 is an important enhancer of IgE production by B cells and plasma cells. This work reinforces the possibility that IL-4 may stimulate the secretion of IgE and IgE binding in AD skin.

"These findings may explain the expression of CD23 by LC (Langerhans cells) and consequently the occurrence of IgE bound to the surface of LC in lesional skin, which in contrast to other dermatoses is characteristic for atopic dermatitis." The authors propose that allergen-driven T-lymphocyte activation in the skin of AD patients leads to binding of IgE to Langerhans cells. They note that the precise mechanisms for tissue damage in AD are not yet known, but may be due to the concurrent release of other cytokines such as IL-5 from stimulated CD4+ T lymphocytes. This paper illustrates the importance of defining the patterns of cytokine responses in skin diseases, and the necessity of combining in vitro functional assays with in situ immunohistochemistry to define the network of cytokines, receptors, antibodies, and antigen-reactive lymphocytes that induce skin disease.

Structural Proteins of the Epidermis Are a Fertile Field for Research in Genetic Diseases of Humans

Structural proteins of the epidermis form a complex cytoskeletal network of intermediate filaments, microtubules and microfilaments, envelope proteins, and adherence junctions that maintain the rigid structure and basic organization of the cells of the epidermis. The relative composition of these proteins and their interrelations help to determine the stratified pattern of the epidermis and the characteristics of the different epidermal layers.

In this issue Ervin Epstein, Jr. and his colleagues at the University of California, San Francisco report the biochemical identification of two cytoskeleton molecules in human keratinocytes, alpha-fodrin, and protein 4.1. They identified immunoreactive forms of both proteins in cultured human keratinocytes, and identified m-RNA transcripts for both proteins, indicating that the proteins were likely synthesized in the epidermis. Calcium shift, which changes expression of m-RNA for differentiation related proteins, had no effect on the alpha-fodrin and protein 4.1 m-RNA. They also were able to clone and sequence the genes for both proteins from human keratinocytes.

Such careful characterization of the genes that code for structural proteins in the epidermis has applications beyond the scientific necessity of understanding the exact biochemical structure of the proteins which determine epidermal structure. Dr. Epstein's interest in the cytoskeletal proteins fodrin and protein 4.1 as potential sites for mutation in inherited diseases has been expanded to studies of mutations in keratins in epidermolysis bullosa (EB). Dr. Epstein noted that "looking for genetic linkage to genes that code for structural proteins in the epidermis has been successful in identifying a keratin point mutation in one epidermolysis bullosa family and a linkage in another family," which may lead to identification of another discreet mutation. This approach has established that the keratins are the likely site of abnormality in some forms of EB. Dr. Epstein notes that proteins such as cytoskeletal proteins, desmosomal proteins and keratins are all candidate genes for mutations in hereditable diseases of the epidermis. The genes for the epidermal proteins alpha fodrin, protein 4.1, involucrin, loricrin, profillagrin, and type I and type II keratins have been cloned and sequenced, and DNA polymorphisms have been identified. Tracing these polymorphisms is one approach to establishing genetic linkage with disease. This pursuit can lead to identification of mutations determining diseases such as epidermolysis bullosa, or perhaps other hereditary disease characterized by disintegration of normal epidermal structure. Dr. Epstein added that careful analysis of such structural proteins in "experiments in nature and in transgenic mice" will be the next challenge in defining the functional significance of the many structural proteins of the epidermis.